REMARKS

REJECTION UNDER 35 USC §103(A) AND REJECTION FOR DOUBLE PATENTING

The rejections of claims 1-7 under 35 USC §103(a) as obvious over Stenzel et al. (US 6,235,281), or for obviousness-type double patenting based thereon, are respectfully traversed. To establish *prima facie* obviousness, the examiner must show in the prior art a teaching or suggestion of each claim element, some suggestion or motivation to make the claimed invention, and a reasonable expectation for success in doing so (*see, e.g., In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). These requirements have not been met in the examiner's present rejection.

The examiner argues that it is obvious from Stenzel to administer TNF antagonists to patients in which interleukin-6 (IL-6) serum levels increase over a measurement period of at least 30 minutes. This argument is supported by Stenzel's disclosure that patients showing elevated IL-6 levels can be treated successfully through administration of TNF antagonists. However, Stenzel makes no reference to temporal fluctuations as a factor in determining whether or not to administer TNF antagonists. The reference simply states that an increased level of success attends such administration when IL-6 levels are elevated. Whether the levels had been dropping or rising is omitted from the disclosure.

The examiner further supports his argument by asserting that

> It is routine in the management of patients with chronic conditions to monitor proinflammatory cytokines (IL-6) as markers over a period of time to determine the change in the levels. This change in IL-6 levels can be measured by a routine mathematical description of the change over time of the level of IL-6. (p.3:16-20)

However, these statements are simple observations. The examiner gives no evidence or reasons to believe that one of ordinary skill in the art would find it obvious to link an observed increase in IL-6 serum levels with success in treatment using TNF antagonists. Without such a link, the examiner's *prima facie* case is incomplete.

In the double patenting rejection, the examiner appears to assert the presence of such a link when he states that "[a]lthough the measurement period is not indicated [in Stenzel], the change in [IL-6] level is clearly indicated" (p.4:10-11). However, the examiner provides no citation to the Stenzel text in support of this assertion, and there is, in fact, no support for this assertion at all in Stenzel. For instance, that reference discloses that

> The treatment of septicemia with TNF antagonists is particularly successful according to this invention ... when the septicemic patients who are treated have IL-6 levels of 500 pg/ml or more *at the start of treatment.* (col.2:15-24, emphasis supplied.)

In the example, Stenzel states that

> It was possible to measure IL-6 serum concentrations *before the start of therapy* in 119 of the 122 patients. The serum levels of IL-6 were >1000 pg/ml in 36 patients and <1000 pg/ml in 83 patients. (col.4:9-12, emphasis supplied.)

These statements from Stenzel demonstrate that only a single reading of IL-6 serum level is taken in determining whether or not to administer TNF antagonists. There is no

suggestion in Stenzel that a change in IL-6 serum level is ever monitored or taken into account in making treatment decisions.

Given that the examiner's argument is missing a nexus between monitoring IL-6 serum levels for increasing value and success in treating with TNF antagonists, the *prima facie* case is incomplete. Applicants respectfully request that both the rejection made under 35 USC §103(a) and that based on the doctrine of obviousness-type double patenting be withdrawn.

REJECTION UNDER 35 USC §112, FIRST PARAGRAPH

The examiner rejects claims 1-3 and 5-7 under 35 USC §112, ¶1 for lack of adequate written description. In making such a rejection, the examiner

> has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. (*In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).)

The examiner asserts that, other than the specifically exemplified anti-TNF antibody fragment MAb 195, it is not apparent that the applicants have possession of the range of TNF antagonists as claimed. However, page 4 of the specification gives numerous examples of TNF antagonists known by those of skill in the art to be effective in the claimed method. Unless the examiner is able to present evidence or reasons why one of skill in the art would not recognize these examples to be representative of all TNF antagonists, the rejection will remain incomplete. The specification references numerous additional sources to give one of skill in the art abundant information

pertaining to the knowledge surrounding TNF antagonists. Applicants respectfully request that the rejection of claims 1-3 and 5-7 for lack of adequate written description be withdrawn.

The examiner further rejects claims 1-3 and 5-7 under §112, ¶1 for lack of adequate enablement. The examiner argues that no evidence exists in the specification demonstrating that TNF antagonists other than MAb 195 is able to treat septic disorders. However, applicants would like to point out to the examiner that the references cited in the specification provide ample support for treatment of septic disorders, in general, with TNF antagonists, in general. The present invention simply adds to this knowledge base by teaching those of skill in the art *when* such treatment would be most effective. The therapeutic value of these basic methods has been demonstrated previously, and applicants would be unnecessarily repeating commonly known prior art, were they to recite examples of all TNF antagonists applied to all septic disorders.

Applicants respectfully submit that the claims are enabled by both the present specification and by the knowledge generally held by one of skill in the art. Applicants further request that the rejection of claims 1-3 and 5-7 under 35 USC §112, ¶1 for lack of adequate enablement, be withdrawn.

CONCLUSION

In view of the foregoing remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

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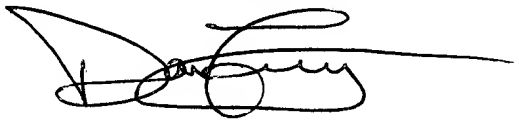
Respectfully submitted,
KEIL & WEINKAUF



David C. Liechty
Reg. No. 48,692

1350 Connecticut Ave., N.W.
Washington, D.C. 20036
(202)659-0100
DCL/mks

COPY OF ALL CLAIMS

1. A method for treating septic disorders where the serum level of interleukin-6 increases in a measurement period of at least thirty minutes, which comprises administering a therapeutically effective amount of a TNF antagonist.

2. The method as claimed in claim 1, wherein the serum level of interleukin-6 is 500 pg/ml and above in the measurement period.

3. The method as claimed in claim1, wherein the measurement period is 4-10 hours.

4. The method as claimed in claim 1, wherein an $F(ab')_2$ fragment of a monoclonal anti-TNF antibody is used as TNF antagonist.

5. A kit comprising a TNF antagonist together with instructions for the use of this TNF antagonist for treating septic disorders where the serum level of IL-6 increases in a measurement period of at least thirty minutes.

6. A kit as claimed in claim 5, wherein a monoclonal anti-TNF antibody is used as TNF antagonist.

7. A method for establishing whether a patient suffering from sepsis is to be treated with TNF antagonists, which comprises the following steps:

   (a) determination of the serum level of interleukin-6 in the patient at a first time t_1,

   (b) determination of the serum level of interleukin-6 at a second time t_2 which is at least 30 minutes after the first time t_1, and determination of the ratio

$$V = \frac{\text{IL-6 level } (t_2)}{\text{IL-6 level } (t_1)}$$

(c) treatment with TNF antagonists in the case where V>1.